

-30-

What is claimed is:

1. An isolated and purified preparation of a combination of a light chain antibody gene and a heavy chain antibody gene, wherein the family members of the light chain antibody gene and the heavy chain antibody gene are selected from the group consisting of V_H4-39/D6-13/J_H5/V_LκO12/2/J_Lκ1/κ2 (Set I), V_H4-34/D5-5/J_H6/V_LκA17/J_Lκ1/κ2 (Set II), V_H3-21/J_H6/V_Lλ3h/J_Lλ3 (Set III), V_H1-69/D3-16/J_H3/V_LκA27/J_Lκ1/κ4 (Set IV), V_H1-69/D3-10/J_H6/V_Lλ1c/J_Lλ1 (Set V), V_H1-02/D6-19/J_H4/V_LκO12/2/J_Lκ1/κ2 (Set VIa), V_H1-03/D6-19/J_H4/V_LκO12/2/J_Lκ1/κ2 (Set VIb), V_H1-18/D6-19/J_H4/V_LκO12/2/J_Lκ1 (Set VIc), V_H1-46/D6-19/J_H4 (Set VId), V_H5-51/D6-19/J_H4/V_LκO12/2/J_Lκ2 (Set VIe), V_H1-69/D3-3/J_H4/V_LκA19/J_Lκ4 (Set VII), and V_H1-69/D2-2/J_H6/V_LκL6/2/J_Lκ3 (Set VIII).
2. The preparation of claim 1, wherein the family members of the light chain antibody gene and the heavy chain antibody gene are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.
3. The preparation of claim 1, wherein the family members of the light chain antibody gene and the heavy chain antibody gene are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.
4. The preparation of claim 1, wherein the family members of the light chain antibody gene and the heavy chain antibody gene are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.
5. The preparation of claim 1, wherein the family members of the light chain antibody gene and the heavy chain antibody gene are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.
6. The preparation of claim 1, wherein the antibody genes are a single chain gene.
7. The preparation of claim 1, wherein the antibody genes are on a vector.
8. The preparation of claim 7, wherein the vector is a cloning vector.
9. The preparation of claim 7, wherein the vector is an expression vector.

10. A cell in culture comprising a vector comprising antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

5 11. The cell of claim 10, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

10 12. The cell of claim 10, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

13. The cell of claim 10, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

15 14. The cell of claim 10, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

20 15. The cell of claim 10, wherein the cell expresses an antibody encoded by the genes.

16. An isolated and purified antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

25 17. The antibody of claim 16, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

30 18. The antibody of claim 16, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

19. The antibody of claim 16, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

-32-

20. The antibody of claim 16, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

5 21. The antibody of claim 16, derived from a hybridoma.

22. The antibody of claim 16, derived from cloned antibody genes.

10 23. The antibody of claim 16, consisting essentially of an Fab, Fab2 or Fv.

24. An anti-idiotypic antibody that binds to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

15 25. The anti-idiotypic antibody of claim 24, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

20 26. The anti-idiotypic antibody of claim 24, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

25 27. The anti-idiotypic antibody of claim 24, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

30 28. The anti-idiotypic antibody of claim 24, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

29. The anti-idiotypic antibody of claim 24, which is a mouse antibody.

30. The anti-idiotypic antibody of claim 24, which is a human antibody.

35 31. The anti-idiotypic antibody of claim 24, which is a humanized antibody.

-33-

32. A bispecific antibody comprising the binding site of the anti-idiotypic antibody of claim 24 and a binding site that binds to another B-cell antigen.

5 33. The bispecific antibody of claim 32, wherein the B-cell antigen is a signal-transducing antigen.

34. The bispecific antibody of claim 32, wherein the B-cell antigen is a surface antigen.

10 35. The bispecific antibody of claim 32, wherein the B-cell antigen is an intracellular antigen.

36. A mixture of two or more of the anti-idiotypic antibodies of claim 24.

15 37. A pharmaceutical composition comprising at least one of the anti-idiotypic antibodies of claim 24, in a pharmaceutically acceptable excipient.

20 38. A peptide antigen that binds to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

25 39. The peptide antigen of claim 38, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

40. The peptide antigen of claim 38, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

30 41. The peptide antigen of claim 38, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

35 42. The peptide antigen of claim 38, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

43. A mixture of two or more of the peptide antigens of claim 38.

44. A pharmaceutical composition comprising at least one of the peptide antigens of claim 38, in a pharmaceutically acceptable excipient.

45. An aptamer that binds to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

46. The aptamer of claim 45, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

47. The aptamer of claim 45, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

48. The aptamer of claim 45, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

49. The aptamer of claim 45, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

50. A mixture of two or more of the aptamers of claim 45.

51. A pharmaceutical composition comprising at least one of the aptamers of claim 45, in a pharmaceutically acceptable excipient.

52. The anti-idiotypic antibody of claim 24, further comprising a cellular toxin.

53. The peptide antigen of claim 38, further comprising a cellular toxin.

54. The aptamer of claim of claim 45, further comprising a cellular toxin.

55. The anti-idiotypic antibody, peptide antigen, or aptamer of any of claims 52-54, wherein the cellular toxin is a radioactive moiety.

5 56. The anti-idiotypic antibody, peptide antigen, or aptamer of any of claims 52-54, wherein the cellular toxin is ricin.

57. The anti-idiotypic antibody, peptide antigen, or aptamer of any of claims 52-54, wherein the cellular toxin is a chemotherapeutic agent.

10 58. The anti-idiotypic antibody of claim of claim 24, further comprising a detectable moiety.

59. The peptide antigen of claim 38, further comprising a detectable moiety.

15 60. The aptamer of claim 45, further comprising a detectable moiety.

61. The anti-idiotypic antibody, peptide antigen, or aptamer of any of claims 58-60, wherein the detectable moiety is a fluorophore.

20 62. The anti-idiotypic antibody, peptide antigen, or aptamer of any of claims 58-60, wherein the detectable moiety is an enzyme.

25 63. A multimeric molecule comprising at least a first and a second binding site, the first binding site binding to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII, and the second binding site binding to either (a) the same antigen-binding region of an antibody as the first binding site or (b) another B-cell antigen.

30 64. The multimeric molecule of claim 63, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

35 65. The multimeric molecule of claim 63, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

66. The multimeric molecule of claim 63, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

5

67. The multimeric molecule of claim 63, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

10

68. The multimeric molecule of claim 63, comprising more than five binding sites.

69. The multimeric molecule of claim 63, wherein all of the binding sites bind to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

15

70. The multimeric molecule of claim 63, wherein all of the binding sites bind to the same epitope.

20

71. The multimeric molecule of claim 63, wherein all of the binding sites are antibody binding sites.

72. The multimeric molecule of claim 63, wherein all of the binding sites are peptide antigens.

25

73. The multimeric molecule of claim 63, wherein all of the binding sites are aptamers.

74. The multimeric molecule of claim 63, wherein the binding sites are a mixture of at least two binding sites selected from the group consisting of an antigen binding site, a peptide antigen, and an aptamer.

30

75. A composition comprising the multimeric molecule of claim 63 in a pharmaceutically acceptable excipient.

35

76. A hybridoma producing the antibody of claim 16.

77. A hybridoma producing the antibody of claim 24.

78. An isolated and purified preparation of a combination of a light chain antibody gene and a heavy chain antibody gene, the gene family members of the light chain antibody gene and the heavy chain antibody gene are present in B cells of two or more patients, wherein the antibody chains of the B cells also share the same isotype, J_H, D and J_L regions, and wherein the B cells are lymphoproliferative in the patient, or wherein the patient has an autoimmune disease involving the B cells.

79. The preparation of claim 78, wherein the patients have B cell chronic lymphocytic leukemia.

80. The preparation of claim 78, wherein the patients have a disorder involving the B cells, the disorder selected from the group consisting of Hodgkin's disease, non-Hodgkin's lymphoma, Burkitt's lymphoma, myeloma, a monoclonal gammopathy with antibody-mediated neurologic impairment, a monoclonal gammopathy of unknown significance, and a monoclonal lymphocytosis of undetermined significance.

81. The preparation of claim 78, wherein the patient has systemic lupus erythematosus, myasthenia gravis, Grave's disease, type I diabetes mellitus, autoimmune peripheral neuropathy, and autoimmune hemolytic anemia.

82. A method of

(a) determining whether a patient with B cell chronic lymphocytic leukemia (B-CLL) has a form of B-CLL susceptible to treatment directed to eliminating idiotype-specific B cell receptor-bearing B-CLL cells, or

(b) following the progression of treatment of B-CLL in a patient having a form of B-CLL susceptible to treatment directed to eliminating idiotype-specific B cell receptor-bearing B-CLL cells,

the method comprising determining whether the B cell receptors on the B-CLL cells have an idiotype encoded by antibody genes from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VIId, Set VIe, Set VII, or Set VIII.

83. The method of claim 82, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, and Set VIII.

5 84. The method of claim 82, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

85. The method of claim 82, wherein the antibody genes are selected from the group consisting of Set II, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VIII.

10

86. The method of claim 82, wherein the antibody genes are selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, and Set VII.

15

87. The method of claim 82, wherein the cells that have B cell receptors that have an idiotype encoded by antibody genes from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, or Set VIII are quantified.

20

88. The method of claim 82, wherein the determination step comprises amplification of idiotype-determining regions of the antibody genes or mRNA and evaluating whether the amplified regions are amplified from the antibody genes of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII or Set VIII.

25

89. The method of claim 88, wherein the evaluation step comprises sequencing the amplified regions.

30

90. The method of claim 88, wherein the evaluation step comprises evaluating whether the amplified regions hybridize with equivalent regions from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII or Set VIII.

35

91. The method of claim 82, wherein the determination step comprises evaluating whether the patient has circulating antibodies with an idiotype encoded by the antibody genes from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, or Set VIII.

92. The method of claim 91, wherein the evaluation step is performed by evaluating whether the patient has antibodies that bind to a binding agent specific for the idiotype encoded by the antibody genes from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, or Set VIII.

5

93. The method of claim 92, wherein the binding agent is an anti-idiotypic antibody, a peptide antigen, or an aptamer.

94. The method of claim 93, wherein the binding agent further comprises a detectable moiety.

10

95. The method of claim 82, wherein the evaluation step is performed by mixing together an agent that binds to the antigen-binding region of an antibody encoded by antibody genes selected from the group consisting of Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII or Set VIII, the agent further comprising a detectable moiety, and

15

lymphocytes of the patient, then
determining whether lymphocytes that bind to the agent are present.

20

96. The method of claim 95, wherein the agent is selected from the group consisting of an anti-idiotypic antibody, a peptide antigen, and an aptamer.

97. The method of claim 95, wherein the determination step utilizes a coulter counter or a flow cytometer.

25

98. The method of claim 82, wherein the patient is pre-leukemic.

99. The method of claim 82, wherein the patient is in an early leukemic state.

30

100. The method of claim 82, wherein the patient is in a frank leukemic state.

101. The method of claim 82, wherein the B-CLL cells from blood of the patient are evaluated.

102. The method of claim 82, wherein the B-CLL cells from the bone marrow, spleen, and/or lymph nodes are evaluated.

103. A method of

5 (a) determining whether a patient with B cell chronic lymphocytic leukemia (B-CLL) has a form of B-CLL susceptible to treatment directed to eliminating idiotype-specific B cell receptor-bearing B-CLL cells, or

10 (b) following the progression of treatment of B-CLL in a patient having a form of B-CLL susceptible to treatment directed to eliminating idiotype-specific B cell receptor-bearing B-CLL cells,

the method comprising determining whether the B cell receptors on the B-CLL cells have an idiotype encoded by antibody genes that fulfill the criteria of the antibody genes described in claim 78.

15 104. A method of treating a patient having B-CLL caused by B cells comprising antibody genes from Set I, Set II, Set III, Set IV, Set V, Set VIa, Set VIb, Set VIc, Set VId, Set VIe, Set VII, or Set VIII, the method comprising administering to the patient an agent that binds to the antigen-binding region of an antibody encoded by the antibody genes.

20 105. The method of claim 104, wherein the agent is selected from the group consisting of an anti-idiotype antibody, a peptide antigen, and an aptamer.

106. The method of claim 104, wherein the agent further comprises a cellular toxin.

25 107. The method of claim 104, wherein the agent binds to more than one antibody encoded by the antibody genes.

108. The method of claim 107, wherein each of the more than one antibody comprises the same antigen-binding region.

30 109. The method of claim 107, wherein the more than one antibody comprises at least two different antigen-binding regions.

110. A method of identifying a B-CLL set, the method comprising identifying the V_H, D, J_H, V_L, and J_L classes of antibody genes present on B-CLL cells, wherein the same classes are all present in more than one B-CLL patient.

5 111. The method of claim 110, further comprising identifying an agent that binds to the antigenic site of an antibody encoded by the antibody genes.

112. The method of claim 111, wherein the agent comprises an anti-idiotypic antibody that binds to the antigenic site of the antibody encoded by the antibody genes.

10

113. The method of claim 111, wherein the agent comprises a peptide antigen that binds to the antigenic site of the antibody encoded by the antibody genes.

114. The method of claim 111, wherein the agent comprises an aptamer that binds to the antigenic site of the antibody encoded by the antibody genes.

15

115. A method of treating a patient having B-CLL caused by B cells comprising antibody genes that fulfill the criteria of the antibody genes described in claim 78, the method comprising administering to the patient an agent that binds to the antigen-binding region of an antibody encoded by the antibody genes.

20

116. A method of determining whether a patient has B-CLL belonging to a set, the method comprising

determining the sequence of the V_H, D, J_H, V_L, and J_L regions of antibody genes of B cell receptors present on the B-CLL cells of the patient,

25

identifying the Ig germline genes having those sequences or closest to having those sequences, and

comparing those identified germline genes with a database of germline genes from other B-CLL patients,

30

wherein the identification of all of the identified germline genes in the database from a B-CLL patient indicates that the patient has B-CLL belonging to a set.